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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/688,069 | 10/14/2000 | Sai S. Subramaniam | 16515.054 | 8450 |

7590

12/18/2002

David Marsh
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EXAMINER

KALLIS, RUSSELL

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1638

DATE MAILED: 12/18/2002

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/688,069

Applicant(s)

SUBRAMANIAM ET AL.

Examiner

Russell Kallis

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 2-9 and 13-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 10-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>9, 10, 11</u> | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1638

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group IV, Claims 1, and 10-12 in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the scope of the claims are so similar that it would not support separate patents. This is not found persuasive because the inventions of Groups I-X are capable of being separately made, independently used, and the patentability of one would not render either of the other obvious or unpatentable.

The requirement is still deemed proper and is therefore made FINAL.

Claim 1 is examined to the extent that it reads on the elected invention, namely an isolated nucleic acid sequence encoding a prokaryotic unifunctional tocopherol cyclase.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims a nucleic acid sequence encoding any prokaryotic tocopherol cyclase and a nucleic acid sequence encoding a tocopherol cyclase from *Synechecystis*.

Art Unit: 1638

Applicant describes a DNA sequence of SEQ ID NO: 38 encoding tocopherol cyclase from *Synechecystis*.

Applicant does not describe any other tocopherol cyclase encoding sequence from *Synechecystis* other than SEQ ID NO: 38 or any other prokaryotic DNA sequences encoding tocopherol cyclases.

Given the claim breadth and lack of guidance as discussed above, the specification does not provide an adequate written description of the claimed invention.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

Claims 1 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Art Unit: 1638

Applicant broadly claims an isolated DNA molecule encoding any prokaryotic tocopherol cyclase.

Applicant teaches the isolation and activity of a DNA encoding a tocopherol cyclase from *Synechecystis* of SEQ ID NO: 38 (Example 6A-D pages 45-46).

Applicant does not teach any other prokaryotic DNA encoding tocopherol cyclase or any other species with sequence homology to SEQ ID NO: 38. In addition, no guidance is provided regarding the particular domains responsible for particular catalytic activities.

The isolation of orthologous DNA sequences from other species introduces an element of unpredictability. The limitation is introduced in finding homologous regions that would adequately enable either PCR amplification or southern hybridization and would entail using either degenerate primers or probes with limited homology. Thus the screen for orthologous sequences would isolate many genes other than those of interest. The inherent unpredictability in isolation of a homologous sequence encoding the same protein activity is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity and that a small number of changes to the coding region of a desaturase could account for the functional divergence seen across a range of enzymes involved in fatty acid metabolism (Broun *et al.* Science Vol. 282 13 November 1998; Abstract lines 4-6 and p. 1317 column 1, lines 51-56).

Computer analysis of genome sequences is currently one of the essential steps for obtaining functional and structural information about the respective gene products, but there are a number of inaccuracies that have been documented by researchers in the field. To illustrate the difficulties, Doerks *et al.*, (TIG, 14: 248-250 1998 pg 248, right column, 2nd paragraph) produces

Art Unit: 1638

a table of BLAST results from an uncharacterized protein family that includes quite a few proteins with annotations. They state "Only one can give a clue about functional features; others are simply wrong, misleading or uninformative". He continues, "There were even examples in which homologues scored best in PSI-BLAST that did not have the same catalytic activity". It is well established that sequence similarity is not sufficient to determine functionality of a DNA coding sequence. Doerks *et al.* state that computer analysis of genome sequences is flawed, and "overpredictions are common because the highest scoring database protein does not necessarily share the same or even similar functions" (the last sentence of the first paragraph of page 248). Doerks *et al.* also teach homologues that did not have the same catalytic activity because active site residues were not conserved (page 248, the first sentence of the last paragraph).

In addition, Smith *et al.* (Nature Biotechnology 15:1222-1223, November 1997) teach "there are numerous cases in which proteins of very different functions are homologous" (page 1222, the first sentence of the last paragraph). Furthermore, Bork *et al.* (TIG 12, 10:425-427, October 1996) teach numerous problems with the sequence databases that can result in the misinterpretation of sequence data. Bork *et al.* discussing the same topic state "search methods are stretched and spurious hits are taken as real. Moreover, similarities might only be restricted to certain domains, but the function is transferred to a whole protein" (pg 426, right column, 1st paragraph).

Further, the unpredictability in predicting enzyme activity with limited information is exemplified in the isolation of *Arabidopsis* tocopherol cyclase that showed not only the one activity observed with the *Synechecystis*, but the tocopherol cyclase enzyme from *Arabidopsis* had two activities; one for phytylplastiquinol and one for geranylgeranylplastiquinol (Porfirova

Art Unit: 1638

et al. PNAS September, 17, 2002, vol. 99, no. 19, pp. 12495-12500 on page 12497 from column 2, line 23 to page 12498 column 2, line 2).

Given the lack of guidance for isolating any other tocopherol cyclase genes or elucidating the required sequence domains for particular catalytic activities, the breadth of the claims, the unpredictability in the art in determining protein activity using homology based methods, and the known errors inherent to functional genomics when relying solely on protein prediction programs, undue trial and error experimentation would be needed by one skilled in the art to isolate and evaluate a multitude of non-exemplified prokaryotic tocopherol cyclase genes.

Therefore the invention is not enabled for the scope set forth in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims are included in the rejection.

Claim 10 recites the limitation "An isolated DNA sequence according to Claim 4, wherein said prokaryotic source" in line 1. There is insufficient antecedent basis for this limitation in Claim 4. Furthermore, there is insufficient antecedent basis for "isolated DNA sequence" in Claim 1, from which Claim 4 depends.

Claim 11 recites the limitation "wherein said tocopherol cyclase" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 recites the limitation "wherein said tocopherol cyclase" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Art Unit: 1638

All claims are rejected.

Claims 1 and 10-12 are deemed free of the prior art, given the failure of the prior art to teach or suggest an isolated DNA molecule encoding any prokaryotic tocopherol cyclase.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the legal analyst, Gwendolyn Payne, whose telephone number is (703) 305-2475.

Russell Kallis Ph.D.
December 9, 2002

DAVID T. FOX
PRIMARY EXAMINER
GROUP 180 / 638

A handwritten signature in black ink, appearing to read "David T. Fox", with a stylized flourish at the end.